IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

NATURAL RESOURCES DEFENSE COUNCIL, INC.,	:	
Plaintiff,	:	
v.	:	10 Civ. 5690 (AKH)
UNITED STATES FOOD AND DRUG ADMINISTRATION; KATHLEEN SEBELIUS, in her official capacity as Secretary, United States Department of Health and Human Services; and MARGARET HAMBURG, in her official capacity as Commissioner, United States Food and Drug Administration,	:	
Defendants.	:	

DECLARATION OF CHARLES J. GANLEY, M.D.

I, Charles J. Ganley, M.D., declare the following:

I. Background

1. I am the Director of the Office of Drug Evaluation and Research IV ("ODE-IV") in the Center for Drug Evaluation and Research ("CDER"), United States Food and Drug Administration ("FDA"), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. ODE-IV is one of six component offices of the Office of New Drugs, which reports directly to CDER's Office of the Center Director.

2. I have been the Director of ODE-IV, and its predecessor, the Division of Over-the-Counter Drug Products, since June 1999. Prior to this position, I was a Medical Officer Team Leader (July 1996 to June 1999) and a Medical Officer (March 1996 to July 1996 and July

1989 to August 1995) in CDER's Division of Cardio-Renal Drug Products. Between August 1995 and March 1996, I was Acting Director, Office of Generic Drugs, CDER, FDA.

3. I received a B.S. degree with highest honors from the University of Pittsburgh in 1976 and an M.D. degree from Hahnemann University in Philadelphia, Pennsylvania, in 1981. I completed an internship and residency in internal medicine at Hahnemann Hospital in 1984 and am board certified in internal medicine. I completed a fellowship in clinical pharmacology at Cornell University Medical Center in 1989. I am licensed to practice as a physician in Maryland.

4. ODE-IV is responsible for the regulation of nonprescription drug products, also referred to as over-the-counter ("OTC") products, and medical imaging drug products. *See* http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm106325.htm. As the Director of ODE-IV, I oversee the regulation of all OTC drug products conducted by two divisions: the Division of Nonprescription Regulation Development ("DNRD") and the Division of Nonprescription Clinical Evaluation ("DNCE"). *Id.* In this capacity, I assist the Director, Office of New Drugs and CDER's Center Director in program and policy developments relating to the "OTC Drug Review" described in detail below. I am familiar with the OTC Drug Review and the status of its progress. I am personally involved with the project including the development of "OTC monographs," also described below, such as the monograph for topical antimicrobial drug products for human use. I have reviewed the complaint filed by the Natural Resources Defense Council, Inc., and I am familiar with the allegations made in this case.

II. Regulation of OTC Drugs

5. OTC drugs play an increasingly vital role in America's health care system by providing easy access to certain drugs that can be used safely without the help of a health care practitioner. Many OTC drug products were first introduced to the market before the 1962

Amendments to the Federal Food, Drug, and Cosmetic Act (the "Act"), which required manufacturers to show that a drug was both safe and effective before it could be legally marketed. Pub. L. No. 87-781, 76 Stat. 780 (1962).

6. After the 1962 Amendments, a manufacturer could seek FDA approval of a prescription or OTC drug by filing a new drug application ("NDA") that showed, among other things, that the drug was safe and effective for each of its intended uses. 21 U.S.C. § 355. FDA also implemented the Drug Efficacy Study Implementation ("DESI"), a retrospective efficacy review of drugs marketed prior to the 1962 Amendments and, consequently, approved only for safety.[1] 37 Fed. Reg. 85 (Jan. 5, 1972) (attached as Exhibit 1). Most of the drugs reviewed in the DESI program were prescription drugs, although approximately 420 were OTC drugs. *Id.*; 21 C.F.R. § 330.12(a).

7. In 1972, after the DESI program was underway, FDA established the OTC Drug Review. 37 Fed. Reg. 9464 (May 11, 1972) (attached as Exhibit 3). The goal of the OTC Drug Review is to establish a "monograph" for each therapeutic class of OTC drug products (*e.g.*, antacids, laxatives, cold remedies). *See* 21 C.F.R. § 330.5 *et seq.* Each monograph specifies acceptable ingredients (including dosage strength, and in some cases, dosage form), labeling (including indications, warnings, and directions for use) and, for some classes, final formulation effectiveness testing. Monographs are developed pursuant to the procedures set forth in FDA regulations, 21 C.F.R. § 330.10 *et seq.*, which provide for an ongoing review of all OTC drugs marketed in the United States. OTC drug products that strictly conform to an applicable monograph are considered to be generally recognized by qualified experts as safe and effective ("GRAS/E") and not misbranded and do not need approval (*e.g.*, through an approved NDA),

[1] DESI was done under contract with the National Academy of Science/National Research Council. 37 Fed. Reg. at 9464 (attached as Exhibit 3).

prior to marketing. 21 C.F.R. § 330.10; 21 U.S.C. §§ 321(p), 355. An OTC drug that does not comply with an applicable monograph generally must have an approved NDA prior to marketing. *See* 21 U.S.C. § 355.

8. The OTC Drug Review has proven to be one of the largest, most complex regulatory undertakings by FDA. It consists of approximately 88 simultaneous rulemakings in 26 broad categories that encompass anywhere from 100,000 to 500,000 OTC drug products marketed in the United States and their some 800 active ingredients and approximately 1,400 different ingredient uses. *See* 21 C.F.R. § 330.5.

9. FDA regulations promulgated in 1972 govern the multi-stage OTC Drug Review. 37 Fed. Reg. 9464 (attached as Exhibit 3). The first, and now completed, stage required the Commissioner to appoint panels of experts comprised of voting members from the scientific community, including physicians, pharmacologists, and toxicologists, and nonvoting members representing the interests of consumers and industry. *See* 21 C.F.R. § 330.10(a). FDA invited the public to submit data and information to the panels pertaining to, among other things, labeling, active ingredients, animal safety data, human safety data, and efficacy data. *Id.* at § 330.10(a)(2). The panels met as often and for as long as was appropriate to evaluate the safety and effectiveness of classes of OTC drugs (categorized by therapeutic category), review the labeling accuracy for such products, and advise the Commissioner on the promulgation of monographs establishing conditions under which drugs within the category are generally recognized as safe, effective, and not misbranded. *Id.* at § 330.10(a)(3). In some instances, the panels held hearings during which the public was afforded an opportunity to present its views. *Id.* Upon completion of their reviews, the panels submitted reports of their conclusions and recommendations to FDA. *Id.* at § 330.10(a)(5).

10. Each panel report classified the drug ingredients in one or more of the following three categories:

- Category I -- conditions under which the drugs are generally recognized as safe and effective and not misbranded;
- Category II -- conditions under which the drugs are *not* generally recognized as safe and effective or are misbranded; or
- Category III -- conditions for which the available data are insufficient to permit final safety and effectiveness classification at the time of the panel's review and for which more testing is required.

Id. at § 330.10(a)(5)(i-iii). An active ingredient could have multiple classifications; for example, it might be Category I for one intended use and Category II for another intended use (*i.e.*, drugs containing that active ingredient might be generally recognized as safe and effective for some intended uses, but not safe and effective for others).

11. The panels' work was much greater than anticipated. Seventeen panels were established to review each broad category of OTC drugs. Some drug categories—such as topical antimicrobial drug products—required review by multiple panels because of their size and complexity. *See, e.g.*, 39 Fed. Reg. 33103 (Sept. 13, 1974) (first antimicrobial panel's conclusions) (attached as Exhibit 6); 47 Fed. Reg. 12480 (Mar. 23, 1982) (second antimicrobial panel's conclusions) (attached as Exhibit 24). In total, the panels reviewed approximately 1,400 active ingredient uses, evaluated more than 14,000 volumes of submitted data and other information, collectively met over 500 times on more than 1,000 days, and deliberated on average 4.5 years each. The panel phase of the OTC Drug Review, which began in 1972, lasted essentially ten years.[2] By 1981, the panels had examined all data, heard witnesses, developed

[2] The original seventeen panels completed their work by 1981, but FDA has since identified several additional categories of OTC drug products recently reviewed by newly formed expert panels. For instance, FDA published a request for data and information on ingredients contained

recommendations (including the classification of drug ingredients), and submitted to FDA reports covering each class of OTC drugs.

12. The second stage of the OTC Drug Review is also complete. At this stage, the Commissioner published in the *Federal Register* an advance notice of proposed rulemaking ("ANPRM") for each category of OTC drugs. 21 C.F.R. § 330.10(a)(6). The ANPRMs contained either the full panel report or a summary of the panel's conclusions and recommendations. *Id.* at § 330.10(a)(6)(iv). The panel's report was not binding on FDA. 37 Fed. Reg. at 9470. The agency was free to disagree with it, comment on difficult issues presented, and request additional information. FDA obtained full public comment on each ANPRM. By 1982, FDA had published ANPRMs for each original class of OTC drugs.

13. During the OTC Drug Review's third stage, the Commissioner develops and publishes a tentative final monograph ("TFM") for each class of OTC drugs. 21 C.F.R. § 330.10(a)(7). A TFM is a proposed rule establishing those conditions for which a class of OTC drugs is generally recognized as safe, effective, and not misbranded. *Id.* Each TFM classifies the drug ingredients into Categories I, II, or III, as defined in paragraph 10 above. An active ingredient is classified as Category II, not Category III, if there is any significant question as to its actual safety.

14. The TFM stage requires considerable agency resources. FDA issues a TFM only after reviewing all comments and any new data submitted to the agency in response to the ANPRM. 21 C.F.R. § 330.10(a)(7)(i). In the preamble to each proposed rule containing a TFM, FDA first presents its views on relevant scientific, medical, policy, and legal issues affecting the

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in products bearing antiplaque-related claims. An advisory review panel completed its review of the data and information submitted, and FDA published the panel's report in the *Federal Register* on May 23, 2003. 68 Fed. Reg. 32232 (attached as Exhibit 37).

category of OTC drugs. By 1994, FDA had issued TFMs for each original category of OTC drugs.

15. After FDA issues a TFM, interested persons such as product manufacturers, consumers, and advocacy groups are afforded extensive procedural protections. Such persons are given a minimum of 90 days (often longer for larger, more complex monographs), to submit written comments or objections to the TFM and to request an oral hearing before the Commissioner.[3] 21 C.F.R. § 330.10(a)(7)(i). Within 12 months after the TFM is published, an interested person may submit new data and information to FDA to support a condition excluded from the TFM. *Id.* at § 330.10(a)(7)(iii). After the final day for submission of new data and information, the rebuttal comment period begins; interested persons may submit new data and information for at least another 60 days. *Id.* at § 330.10(a)(7)(iv). Given the lengthy comment and rebuttal periods, FDA often receives extensive, voluminous, and conflicting comments and new data and information after publishing a TFM. FDA's work does not stop there, as the agency frequently receives new data and information after the comment and rebuttal periods close. Upon a showing of good cause, the Commissioner may consider new data and information thereafter. 21 C.F.R. § 330.10(a)(7)(v).

16. During the fourth stage of the OTC Drug Review, FDA issues final monographs. 21 C.F.R. § 330.10(a)(9). A final monograph is a final rule that establishes conditions under which the category of OTC drugs is generally recognized as safe and effective and not misbranded. *Id.* Category II and III conditions (like active ingredients) are excluded from the final monograph, or become "nonmonograph conditions." Before a final monograph issues,

[3] After reviewing objections filed in response to the TFM, an oral hearing may be scheduled before the Commissioner. 21 C.F.R. § 330.10(a)(8).

however, FDA expends significant resources to review and evaluate all comments, data, and information submitted after publication of the TFM, as described above, together with the entire record. For certain monographs, like the monograph for topical antimicrobial drug products, the comments, data, and information often relate to complex scientific, medical, policy, and legal issues. When all such issues have been resolved by the appropriately trained FDA employees, DNRD prepares a draft document that analyzes the issues, responds to public comments raised, and drafts the final monograph for the relevant class of OTC drugs. The draft is then routed to various components within FDA for scientific and medical review, consistency of policy, and legal sufficiency.

17. After FDA components weigh in, any differences are resolved. Before issuing a final monograph, FDA must be certain that it is consistent with existing regulations involving other drugs and products regulated by FDA. The monographs must also be consistent with each other in areas such as combinations of, and appropriate doses of, OTC drugs covered by more than one monograph, and they must be consistent with FDA's treatment of prescription drugs.

18. When this process is completed, a final version of the monograph is prepared for endorsement by various components within the agency and ultimately the Commissioner of Food and Drugs. Once the document is endorsed by the Commissioner, it is reviewed by the Department of Health and Human Services ("HHS") and, for some monographs, the Office of Management and Budget ("OMB"). These agencies may raise issues that may require referral back to FDA for resolution. After full review, the document is published in the *Federal Register*.[4]

[4] TFMs also undergo a similarly thorough review process.

19. Because the monographs are based on scientific evidence and evaluation, which can evolve and change over time, in many instances FDA must reissue a TFM before publishing final monograph to resolve newly emerging, often complex issues through public participation. For example, FDA reissued the laxative TFM to reflect new information on dosage strength and directions for use. 51 Fed. Reg. 35, 136 (Oct. 1, 1986) (attached as Exhibit 27). FDA published a new antihistamine TFM to address new ingredients and changes to required warnings. 52 Fed. Reg. 31,892 (Aug. 24, 1987) (attached as Exhibit 28). When FDA reproposes a TFM, it must permit time for a new round of notice and comment.

20. At each stage of the OTC Drug Review, the panel and the Commissioner must apply safety, effectiveness, and labeling standards, as set out in the regulations. 21 C.F.R. § 330.10(a)(4). Because each category of OTC drugs has distinct characteristics, FDA's analysis of the applicable standards differs by drug category.

21. The OTC Drug Review is never officially complete for any particular product class. After publication, a final monograph may be amended, either on the Commissioner's own initiative or upon the petition of any interested person. 21 C.F.R. § 330.10(a)(2). OTC drug monographs are continually updated to add ingredients, labeling, or other pertinent information, as needed.

22. The Nonprescription Drugs Advisory Committee ("NDAC"), an advisory review committee formed by FDA and whose members include experts from outside FDA, also plays a vital role in the review and evaluation of issues affecting TFMs and final monographs. *See* 21 C.F.R. 14.100(c)(17). NDAC meets regularly to assist the agency in evaluating safety, effectiveness, and proper labeling of OTC drug products. Replacing the advisory review panels

used during the first phase of the OTC Drug Review, which disbanded as their work was completed, NDAC considers issues of importance as they arise.

23. ODE-IV's DNRD is primarily responsible for administering the OTC Drug Review. However, physicians, scientists, statisticians, and regulators throughout CDER, attorneys in the Office of Chief Counsel, and other Centers within FDA are continuously involved in this massive endeavor. FDA also collaborates with other components of HHS and other federal agencies, as needed.

24. Among other responsibilities, DNRD evaluates and analyzes data and information submitted for each monograph during the lengthy, and often extended, comment and rebuttal periods. In doing so, DNRD reviews and assesses scientific data and other information pertaining to the safety, effectiveness, and proper labeling of each class of OTC drugs and identifies areas in which additional data and information are needed. This often requires the resolution of large numbers of complex medical, scientific, policy, and legal issues in such areas as ingredient classification, drug testing and formulation, and drug labeling, among others. DNRD then drafts or reissues TFMs, final monographs, and amendments to final monographs. As needed, DNRD coordinates NDAC meetings and provides technical assistance on OTC compliance matters to CDER's Office of Compliance.

25. In total, the OTC Drug Review requires immensely time- and labor-intensive work and considerable agency resources. Anything less would compromise the scientific integrity of the OTC Drug Review.

III. Active Ingredients Removed From the Marketplace to Protect Public Health and FDA's Enforcement Discretion

26. Since the inception of the OTC Drug Review, FDA has firmly maintained the position that the agency will not hesitate to take action, if warranted even before a monograph is

final, to ban ingredients that pose a threat to public health. When active ingredients are identified as unsafe, FDA removes them from the OTC marketplace by *Federal Register* notice.

27. Some notable examples include hexachlorophene, an active ingredient used in topical antimicrobial skin cleanser products, 37 Fed. Reg. 219 (Jan. 7, 1972) (attached as Exhibit 2), 37 Fed. Reg. 20160 (Sept. 27, 1972) (attached as Exhibit 5), codified at 21 C.F.R. § 250.250; TBS, an antibacterial ingredient, 39 Fed. Reg. 33102 (Sept. 13, 1974) (attached as Exhibit 6), 40 Fed. Reg. 50527 (Oct. 30, 1975) (attached as Exhibit 10), codified at 21 C.F.R. § 310.508; zirconium, an antiperspirant ingredient, 40 Fed. Reg. 24328 (June 5, 1975) (attached as Exhibit 9), 42 Fed. Reg. 41374 (Aug. 16, 1977) (attached as Exhibit 13), codified at 21 C.F.R. § 310.510; chloroform, 41 Fed. Reg. 15026 (Apr. 19, 1976) (attached as Exhibit 11), 41 Fed. Reg. 26842 (June 29, 1976) (attached as Exhibit 12), codified at 21 C.F.R. § 310.513; and sweet spirits of nitre, used to reduce fevers in infants, among other uses, 45 Fed. Reg. 43400 (June 27, 1980) (attached as Exhibit 21), codified at 21 C.F.R. § 310.502. FDA went even further for the category of active ingredients intended for use as OTC daytime sedatives, concluding that no ingredients labeled for such use are generally recognized as safe and effective. 44 Fed. Reg. 36378 (June 22, 1979) (attached as Exhibit 17). FDA also has banned active ingredients for which the agency lacks adequate data to establish general recognition of the safety and effectiveness for specified uses and for which no new data are available. *E.g.*, 55 Fed. Reg. 46914 (Nov. 7, 1990) (attached as Exhibit 30); 58 Fed. Reg. 27636 (May 10, 1990) (attached as Exhibit 32a); 67 Fed. Reg. 31123 & 31125 (May 9, 2002) (attached as Exhibit 36), codified at 21 C.F.R. § 310.545.

28. FDA generally exercises its enforcement discretion to permit OTC drug products that do not have an approved NDA to be marketed during the pendency of the OTC Drug

Review provided that four conditions are met: (1) the drug product or similarly formulated and labeled products were marketed as OTC drugs at the inception of the OTC Drug Review; (2) the drug product does not constitute a hazard to health; (3) the drug product is not a prescription drug within the meaning of 21 U.S.C. § 323(b); and (4) the drug product is an OTC drug and does not bear claims for serious disease conditions that require the attention and supervision of a licensed practitioner. 68 Fed. Reg. 75585, 75590-91 (Dec. 31, 2003) (attached as Exhibit 38). The agency, however, has confirmed through the issuance of guidance documents that it will take regulatory action against an OTC product if the agency believes that the product poses a health hazard to consumers or otherwise violates the Act. Compliance Policy Guide Sec. 450.200, Drugs - General Provisions and Administrative Procedures for Recognition as Safe and Effective, http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidance Manual/ucm074388.htm; Compliance Policy Guide Sec. 440.100 Marketed New Drugs Without Approved NDAs and ANDAs, http://www.fda.gov/ICECI/ComplianceManuals/Compliance PolicyGuidance Manual/ucm074382.htm.

IV. Challenges Affecting the OTC Drug Review's Progress

29. In the absence of accurate estimates of the size of the endeavor, and with a sincere desire to complete the project as expeditiously as possible, in retrospect, FDA was overly optimistic about how long the OTC Drug Review would take. For instance, in 1972, FDA understood that most drugs subject to review were compounded from 200 active ingredients, when, in fact, the OTC Drug Review eventually encompassed some 800 active ingredients (plus combinations of those ingredients), many in different drug products with varying intended uses.[5]

[5] Each active ingredient differs based on a variety of characteristics (*e.g.*, chemical, structure, mode of action, spectrum of antimicrobial activity, absorption through the skin, time to effect, duration of effect, etc.).

See 37 Fed. Reg. 85, 86 (attached as Exhibit 1); *see also* 37 Fed. Reg. 9474 ("The [FDA] believes that the therapeutic category approach to OTC drugs is appropriate, since there are only an estimated 200 active ingredients in the thousands of OTC drugs now marketed . . . .") (attached as Exhibit 3). Another challenge FDA faced was a paucity of quality scientific evidence in medical literature available for review by the advisory review panels in reaching final conclusions on general recognition of safety and effectiveness.

30. Not every monograph could realistically be issued at once. FDA's first priority was to complete the advisory panel reviews for all categories and publish their reports. FDA then focused its attention on issuing TFMs for each category, followed by final monographs.[6]

31. Despite the agency's progress, over the years, the OTC Drug Review required more work and additional resources than anticipated, which has affected the length of time needed to finalize all monographs. Most monographs have evolved significantly since the beginning of the OTC Drug Review, often due to issues revealed by emerging science and impacting FDA's analysis of safety, effectiveness, and labeling. FDA has bifurcated many monographs into separate subcategories; each subcategory involves distinct issues and considerations for safety, effectiveness, and labeling. Accordingly, each is considered as a separate rulemaking (and requires separate tentative final and final monographs). For administrative efficiency, FDA has merged other monographs into a single monograph. Often FDA has faced policy and legal decisions that greatly impact one or more monographs and need to be resolved before taking action.

32. Legal challenges were among other factors contributing to the length of the OTC Drug Review. During the panel phase, FDA responded to a lawsuit challenging the procedures

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[6] *See* paragraph 11, note 1.

under which the panel meetings were conducted. *Smart v. FDA*, Civ. No. C-73-118-RHS (N.D. Cal., Apr. 24, 1974).

33. In another lawsuit, the District Court for the District of Columbia invalidated FDA's regulations permitting continued testing of Category III ingredients after issuance of a final monograph. *Cutler v. Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). FDA then amended its regulations to comply with that decision. 44 Fed. Reg. 61608 (Oct. 26, 1979) (attached as Exhibit 18), 45 Fed. Reg. 31422 (May 13, 1980) (attached as Exhibit 20), 46 Fed. Reg. 47739 (Sept. 29, 1981) (attached as Exhibit 22). The revised regulations no longer permit marketing of Category III ingredients after publication of a final monograph. Instead, all testing of Category III ingredients to resolve safety or effectiveness issues and FDA decisions on those ingredients generally now must be reached before, rather than after, publication of the final monograph. 59 Fed. Reg. 31402, 31403 (June 17, 1994) (attached as Exhibit 34). 21 C.F.R. § 330.10. In September 1981, FDA published a policy statement announcing that it would meet with industry representatives to discuss study protocols and test results for Category III ingredients, and promised to comment on the adequacy of study results to upgrade an ingredient to Category I while it was being considered as part of the monograph process. 46 Fed. Reg. 47740 (Sept. 29, 1981) (attached as Exhibit 22). These changes significantly affected the OTC Drug Review's procedures, added new steps to the review process, and required careful consideration along with a concomitant expenditure of time and resources.

34. In addition to legal challenges to the OTC Drug Review's procedures, FDA was in litigation over the pace of the OTC Drug Review for most of the 1980s. *Cutler v. Hayes*, 818 F.2d 879 (D.C. Cir. 1987). After an appeal to the U.S. Court of Appeals for the District of Columbia Circuit, the U.S. District Court for the District of Columbia ultimately decided that

case in favor of FDA and finally dismissed it in September 1995. *Cutler v. Hayes*, Civ. No. 81-2092 (TPJ) (D.D.C, Sept. 7, 1995) (attached as Exhibit 42).

35. During the OTC Drug Review, FDA has and continues to prioritize its limited agency resources. On an ongoing basis, DNRD assists DNCE in reviewing NDAs for OTC drugs. Among other responsibilities, DNRD and DNCE also collaborate in:

- **Responding to Citizen Petitions:** For example, in April 2009, FDA responded at length to multiple Citizen Petitions requesting FDA to reopen the record and amend the TFM for Health-Care Antiseptic Drug Products to include sodium hypochlorite at various concentrations and for certain uses. In April 2010, after further review, FDA denied a subsequent request to reconsider those Citizen Petitions;
- **Monitoring Medication Error Reports:** Medication errors are preventable events that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. For example, in February 2010, FDA warned consumers about choosing the wrong liquid Maalox product for their condition after receiving five reports of related serious medication errors. *See* http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm199331.htm; and
- **Issuing Public Safety Alerts and Providing Drug Safety Information to Health Professionals:** For example, in 2006, FDA issued a health alert on the risk of methemoglobinemia associated with benzocaine used in sprays as a localized numbing agent. *See* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124350.htm. In 2008, FDA issued a health alert and provided healthcare professionals with updated information on the risks associated with the use of oral sodium phosphates for bowel cleansing. *See* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103354.htm. FDA also issued earlier safety alerts for these products, such as *Science Backgrounder: Safety of Sodium Phosphates Oral Solution*, a paper FDA published in 2001. *See* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm173897.htm. In 2006, FDA issued a health alert and a second science background paper, addressing a rare but serious form of kidney failure associated with the use of oral sodium phosphate products for bowel cleansing. *See* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161581.htm.

Additionally, ODE-IV is responsible for addressing known safety issues involving OTC drugs such as issues associated with pain relievers and fever reducers, including acetaminophen; drug tampering, and the use of oral sodium phosphate products for bowel cleansing discussed above.

36. FDA's work on OTC drugs is part of the agency's overall commitment to regulate human and animal drugs, one component of FDA's regulatory responsibilities. The agency is also responsible for regulatory oversight of food, medical devices, biologics, and most recently tobacco products.[7] *See* FDA's strategic priorities for 2011 through 2015, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/StrategicActionPlan/UCM226907.pdf.

V. OTC Drug Review's Progress

37. Despite the many challenges discussed above, FDA has made significant strides in advancing the OTC Drug Review. The agency has issued final monographs for the majority of OTC drug categories, which are published in the Code of Federal Regulations at 21 C.F.R. Parts 331-358. As of December 1, 2010, FDA has published over 150 proposed rules (including, TFMs, amended TFMs, and proposed rules to amend final monographs) and 130 final rules (including final monographs and amended final monographs). From 1982 to 2010, FDA published, on average, 9 proposed and final rules annually as part of the OTC Drug Review:

Table 1. OTC Drug Review *Federal Register* notices published annually (1972-2010)

Time Period	Proposed Rules		Final Rules		Total	
	Actual Number	Annual Rate†	Actual Number	Annual Rate†	Actual Number	Annual Rate†
1972-1981	8	0.8	7	0.7	15	1.5
1982-1988	48	6.9	15	2.1	63	9.0
1989-2010	95	4.3	103	4.7	198	9.0

[7] The 2009 Family Smoking Prevention and Tobacco Control Act gave FDA the authority to regulate tobacco products.

† Equals number of rules published divided by number of years during specified time period.

FDA's website provides a detailed status of all rulemakings. *See* Milestone Status Documents, available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ Development Resources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/default.htm.

VI. Monograph for Topical Antimicrobial Drug Products

38. The monograph for topical antimicrobial drug products for OTC human use is one of the largest, most complex, and controversial of the monographs. The monograph encompasses the entire class of OTC topical antimicrobial drug products, many of which contain the same active ingredients but are labeled and marketed for different intended uses. Antimicrobial drug products are used to kill or inhibit the growth of microorganisms, such as bacteria. Antimicrobials include antiseptics and both natural and synthetic antibiotics.

39. The monograph's rulemakings affect a vast array of OTC drug products with a significant impact, and historically have generated a great deal of interest. As a result, FDA has granted generous extensions to the comment and rebuttal period at virtually every step of this rulemaking, *e.g.*, 39 Fed. Reg. 33103 (Sept. 13, 1974) (attached as Exhibit 6), 43 Fed. Reg. 4637 (Feb. 3, 1978) (attached as Exhibit 15), 59 Fed. Reg. 58799 (Nov. 15, 1994) (attached as Exhibit 35), and found good cause to reopen the administrative record numerous times to include new data and information submitted after the comment and rebuttal periods closed, *e.g.*, 44 Fed. Reg. 13041 (Mar. 9, 1979) (attached as Exhibit 16), 44 Fed. Reg. 61609 (Oct. 26, 1979) (attached as Exhibit 18), 45 Fed. Reg. 18398 (Mar. 21, 1980) (attached as Exhibit 19), 47 Fed. Reg. 436 (Jan. 5, 1982) (attached as Exhibit 23), 47 Fed. Reg. 22324 (May 21, 1982) (attached as Exhibit 25), 68 Fed. Reg. 75585 (Dec. 31, 2003) (attached as Exhibit 38). Interest in this monograph remains

peaked, as the rulemaking process continues to generate a considerable number of data submissions and other information.

40. Because of its size and complexity, several advisory review panels convened to consider drug products covered by the monograph for topical antimicrobial drug products. After requesting data and information from the public, 37 Fed. Reg. 235 (Jan. 7, 1972) (attached as Exhibit 4), 37 Fed. Reg. 6775 (Apr. 4, 1972) (attached as Exhibit 4a), the first antimicrobial advisory review panel convened for a total of 35 days over a one and a half year period. FDA published that panel's report in an ANPRM in September 1974. 39 Fed. Reg. 33103 (Sept. 13, 1974) (attached as Exhibit 6). After numerous requests, FDA granted two extensions to the ANPRM's public comment period, in part because of the complexity of the panel's report. 39 Fed. Reg. 35675 (Oct. 3, 1974) (attached as Exhibit 7); 39 Fed. Reg. 37066 (Oct. 17, 1974) (attached as Exhibit 8). After addressing and analyzing issues containing in over 100 public submissions, FDA issued the first TFM for topical antimicrobial drug products ("1978 TFM"). 43 Fed. Reg. 1210 (Jan. 6, 1978) (attached as Exhibit 14). In February 1980, a second advisory review panel submitted its panel report to FDA after meeting to review additional antimicrobial drug products. *See, e.g.*, 47 Fed. Reg. 12480 (Mar. 23, 1982) (ANPRM based on recommendations of second antimicrobial advisory review panel) (attached as Exhibit 24). The second antimicrobial panel was one of the longest-running panels, conducting 54 meetings lasting a total of 128 days over 6.5 years. Additionally, during the early 1980s, FDA received recommendations pertaining to topical antimicrobial products from different panels and reopened the administrative record for the topical antimicrobial monograph to review these recommendations. *See, e.g.*, 47 Fed. Reg. 436 (Jan. 5, 1982) (attached as Exhibit 23); 47 Fed.

Reg. 22324 (May 21, 1982) (attached as Exhibit 25); 47 Fed. Reg. 39406 (Sept. 7, 1982) (attached as Exhibit 26).

41. Since FDA issued the 1978 TFM, the scope and structure of the monograph for topical antimicrobial drug products has changed drastically. As originally conceived and tentatively proposed in the 1978 TFM, FDA planned to publish one final monograph covering all topical antiseptic drug products, which are used to kill or inhibit the growth of microorganisms on the skin. However, in the early 1980s, FDA merged other, related therapeutic categories with the topical antimicrobial drug monograph. *See also, e.g.*, 47 Fed. Reg. 436 (Jan. 5, 1982) (adding 18 more active ingredients to the antimicrobial rulemaking) (attached as Exhibit 23); 47 Fed. Reg. 12480 (Mar. 23, 1982) (ANPRM for antifungal drug products) (attached as Exhibit 24); 47 Fed. Reg. 22324 (May 21, 1982) (adding four more active ingredients to the antimicrobial rulemaking) (attached as Exhibit 25). Although administratively efficient, this created additional subcategories by therapeutic use and more active ingredients to consider under the topical antimicrobial monograph. *Id.* FDA thereafter finalized portions of the monograph. *See* 52 Fed. Reg. 47312 (Dec. 11, 1987) (final monograph for antibiotic drug products) (attached as Exhibit 29); 56 Fed. Reg. 41008 (Aug. 16, 1991) (acne drug products) (attached as Exhibit 32); 58 Fed. Reg. 49890 (Sept. 23, 1993) (antifungal drug products) (attached as Exhibit 33). Because of its size and complexity, FDA divided other portions of the original monograph into subparts so that the agency could separately assess safety, effectiveness, and proper labeling for the range of different uses of antimicrobial drug products. *See* 59 Fed. Reg. 31402, 31403 (June 17, 1994) (attached as Exhibit 34). FDA determined that it was appropriate to reissue TFMs and final monographs for new subcategories. *Id.* For example, in 1991, FDA issued a TFM for First Aid Antiseptic Drug Products, 56 Fed. Reg. 33644 (July 22, 1991) (attached as Exhibit 31),

followed by a TFM for Health-Care Antiseptic Drug Products in 1994. 59 Fed. Reg. 31402 (June 17, 1994) (attached as Exhibit 34).

42. The monograph for topical antimicrobial drug products is currently comprised of six subparts:

a. First Aid Antiseptic Drug Products;
b. First Aid Antibiotic Drug Products;
c. Antifungal Drug Products;
d. Acne Drug Products;
e. Health-Care Antiseptic Drug Products; and
f. Diaper Rash Drug Products.

Because each subcategory functions as its own monograph, FDA must publish separate TFMs and final monographs for each. FDA has promulgated final monographs for First Aid Antibiotic Drug Products, Topical Antifungal Drug Products, and Topical Acne Drug Products. These final monographs are codified at 21 C.F.R. Part 333, Subparts B through D.

43. Finalizing the rulemaking for Health-Care Antiseptic Drug Products is currently one of the highest priorities of the OTC Drug Review. The 1994 TFM for Health-Care Antiseptic Drug Products ("1994 TFM") encompasses antiseptic drug products marketed for use by health care professionals (*e.g.*, health care personnel handwashes, patient preoperative skin preparations, surgical hand scrubs) and consumers (*e.g.*, handwashes for personal use in the home) and requested data about antiseptic drug products marketed for use by food handlers. 59 Fed. Reg. 31402 (attached as Exhibit 34). Since that time, FDA has determined that these settings differ in important ways. For instance, in the hospital setting, the risk of exposure to pathogenic bacteria is high within a population that includes many individuals with weakened immune systems and an increased risk for serious infections. In the consumer setting, by

contrast, the target population is comprised of generally healthy individuals and the risk of infection is relatively low.

44. Because the risks and benefits are typically very different between these populations, FDA plans to reissue the 1994 TFM in multiple parts, addressing topical antiseptic drugs products intended for use by consumers, health care workers, and food handlers separately. *Semiannual Regulatory Agenda*, 75 Fed. Reg. 21781, 21793 (Apr. 26, 2010) (attached as Exhibit 39). Reflecting this change, the restructured monograph for topical antimicrobial drug products might be addressed separately for different product categories, for example:

a. First Aid Antiseptic Drug Products;
b. First Aid Antibiotic Drug Products;
c. Antifungal Drug Products;
d. Acne Drug Products;
e. Non-First Aid Antiseptic Drug Products, including
    1. Consumer Antiseptic Drug Products;
    2. Health-Care Antiseptic Drug Products; and
    3. Food Handler Antiseptic Drug Products; and
f. Diaper Rash Drug Products.

By restructuring the monographs, FDA will be able to separately assess and analyze the unique risk-benefit profile for each antiseptic use. However, separate analytical review will require the agency to further subdivide the monograph, and the agency will likely issue new proposed and final rules for Consumer Antiseptic, Health-Care Antiseptic, and Food Handler Antiseptic Drug Products.

45. FDA has publicly announced its plans to issue a proposed rule for Consumer Antiseptic Drug Products. *See Semiannual Regulatory Agenda*, 75 Fed. Reg. at 21793 (attached

as Exhibit 39). FDA intends to issue a proposed rule on consumer antiseptics or take other regulatory action as soon as practicable.

46. DNRD chose to draft the proposed rule for Consumer Antiseptic Drug Products before the other antiseptic subcategories for several reasons. After FDA published the 1994 TFM, but particularly since 2005, concerns have emerged about whether increased exposure to certain antimicrobial active ingredients, such as triclosan and triclocarban, that are present in many consumer products is safe for humans. FDA determined that the agency should first address Consumer Antiseptic Drug Products, which include antimicrobial soaps, antiseptic handwashes, and antiseptic hand rubs (sometimes referred to as hand sanitizers) that are intended for daily use by the public. FDA plans to incorporate the most up-to-date data and information into the proposed rule and to ensure that any data supporting the monograph meet FDA standards for safety and effectiveness.[8]

VII. Triclosan and Triclocarban

47. Triclosan and triclocarban are antimicrobial active ingredients that may be added to a variety of products and applications to reduce or prevent bacterial contamination. Triclocarban, and more commonly triclosan, may be used as a preservative in cosmetics and as an antiseptic active ingredient in certain consumer products (*e.g.*, soaps and toothpastes) and healthcare professional products (*e.g.*, healthcare personnel handwashes and surgical handscrubs).[9] Because these substances are used in a wide variety of consumer products, it is

[8] FDA's work on the proposed rule for Consumer Antiseptic Drug Products will have an impact on safety, effectiveness, and labeling considerations for other antimicrobial categories.

[9] Triclosan has a wide-variety of other uses not pertinent to the OTC Drug Review, *i.e.*, as a disinfectant in household products (*e.g.*, cleansers, plastics, and textiles) and to inhibit bacterial growth on medical devices (*e.g.*, sutures and stents) and in commercial and industrial applications (*e.g.*, conveyor belts, ice machines).

challenging to conduct meaningful studies that can accurately characterize exposure to these chemicals in all settings where it occurs.

48. Triclosan and triclocarban are two of the twenty-six active ingredients that FDA considered under the 1994 TFM. 59 Fed. Reg. at 31435-31436, Tables 1 and 2 (attached as Exhibit 34). The 1994 TFM classified triclosan as a Category III active ingredient for safety and effectiveness (*i.e.*, insufficient information/more testing required to determine general recognition of safety and effectiveness), and triclocarban as a Category I ingredient for safety (*i.e.*, generally recognized as safe) and a Category III ingredient for effectiveness.

49. FDA's consideration of triclosan and triclocarban is not limited to the OTC Drug Review. FDA has evaluated the safety and effectiveness of certain drug products containing triclosan and triclocarban, and FDA has approved NDAs for drug products containing these ingredients. For instance, in 1997, FDA approved an NDA for Colgate Total Toothpaste, a product containing triclosan.

50. When consumers use drug products containing triclosan or triclocarban, they may be exposed to these substances, for example by absorbing small amounts through the skin (*e.g.*, handwash) or in the mouth (*e.g.*, toothpaste). A recent study by the Centers for Disease Control and Prevention ("CDC") found measurable amounts of triclosan in the urine of study participants, but CDC has not concluded that such levels adversely affect human health:

> [f]inding measurable amounts of triclosan in urine does not mean that the levels of triclosan cause an adverse health effect. Biomonitoring studies on levels of triclosan provide physicians and public health officials with reference values so that they can determine whether people have been exposed to higher levels of triclosan than are found in the general population. Biomonitoring data can also help health scientists plan and conduct research on exposure and health effects.

http://www.cdc.gov/exposurereport/Triclosan_FactSheet.html.

51. At this time, data submitted and otherwise available to FDA support the continued consideration of triclosan and triclocarban under the ongoing topical antimicrobial monograph proceedings. *See also Triclosan: What Consumers Should Know*, http://www.fda.gov/forconsumers/consumerupdates/ucm205999.htm. FDA, however, intends to continue to evaluate concerns associated with triclosan and triclocarban and address the safety and effectiveness of all consumer antiseptic active ingredients through rulemaking as soon as practicable.

VIII. New Scientific Developments Affecting Antiseptic Drug Products, Including Those that Contain Triclosan and Triclocarban

52. In recent years, new scientific developments have altered FDA's previous safety and effectiveness considerations for triclosan and triclocarban, as well as some of the other 24 active ingredients in antiseptic drug products. A close examination of these developments, changes in patterns of use for antiseptic drug products, and potential environmental concerns, prompted FDA to reevaluate its tentative conclusions in the 1994 TFM for Health-Care Antiseptic Drug Products. FDA's work on the rulemaking, and on these two active ingredients in particular, is substantial and ongoing. The agency must continue to actively examine the complex and developing body of scientific research on the safety and effectiveness of triclosan and triclocarban, among other active ingredients.

A. Endocrine Disruption

53. One new potential safety concern pertains to the potential effects of triclosan and triclocarban and other active ingredients as endocrine disruptors. Endocrine disruptors ("EDs") are external substances that disrupt the normal function of the endocrine system. EDs may affect hormone systems, such as the androgen, estrogen, or thyroid hormone systems.

54. The scientific community published its first study on triclosan and endocrine disruption in July 2000. C.M. Foran et al., *Developmental Evaluation of a Potential Non-Steroidal Estrogen: Triclosan*, Marine Envtl. Research 153 (2000) (attached as Exhibit 44). In the intervening years, newly available scientific literature on the endocrine disrupting potential of antiseptic ingredients has come to FDA's attention, particularly beginning in 2005. Scientific research on the subject is in its very early stages and the science underlying endocrine disruption and antimicrobial active ingredients is evolving. FDA believes that existing data raise valid concerns about the effects of repeated daily human exposure to antiseptic ingredients such as triclosan and triclocarban. FDA detailed its concerns in a response to an inquiry from Congressman Edward J. Markey in February 2010. Although public interest on the subject is high, existing data suggesting that triclosan may act as an endocrine disruptor are still very preliminary. Even fewer endocrine-related studies exist for triclocarban.

55. The United States Environmental Protection Agency ("EPA") has recently established an Endocrine Disruptor Screening Program ("EDSP"). Through EDSP, "EPA is developing requirements for the screening and testing of pesticides, commercial chemicals, and environmental contaminants for their potential to disrupt the endocrine system." http://www.epa.gov/endo/pubs/edspoverview/background.htm. EPA also faces challenges in making regulatory determinations with respect to new and emerging scientific evidence on endocrine disruption including a lack of available scientific data and validated testing methods -- as explained on EPA's website:

> Although EPA has some data on endocrine-disrupting pesticides, insufficient scientific data are available for most of the chemicals produced today to allow for an evaluation of endocrine associated risks. The science related to measuring and demonstrating endocrine disruption is relatively new and validated testing methods are still being developed.

http://www.epa.gov/endo/pubs/edspoverview/background.htm.

56. To better understand the endocrine disrupting potential of antiseptic active ingredients including triclosan and triclocarban, FDA has been collaborating with EPA to assess the potential for endocrine disruption for substances that fall within the agencies' concurrent jurisdictions. In February 2010, FDA discussed the agencies' collaborative efforts in a letter to Congressman Edward J. Markey. FDA explained that the agencies are working on research projects that will help both agencies better characterize the endocrine-related effects of triclosan. In that letter, FDA also represented that its ongoing information exchange with EPA continues to provide a framework for implementing changes to the 1994 TFM. *See* Letter from Jeanne Ireland, Assistant Commissioner for Legislation, FDA, to the Honorable Edward J. Markey, dated February 23, 2010 (attached as Exhibit 11 to Declaration of Vivian Wong, counsel for NRDC, dated September 23, 2010). EPA recently acknowledged the agencies' ongoing cooperative efforts related to triclosan. 75 Fed. Reg. 76461, 76463 (Dec. 8, 2010) ("[EPA] is aware of FDA's ongoing effort to finalize the topical antimicrobial [OTC] drug monograph under which some products containing triclosan are regulated. EPA and FDA intend to collaborate and share information [on triclosan related matters including] FDA's ongoing rule development.") (attached as Exhibit 41).

57. Various components of HHS, other Centers within FDA, and nongovernment organizations recently have begun to monitor and evaluate scientific developments pertaining to endocrine disruption. In February of this year, Dr. Linda S. Birnbaum, Director of the National Institutes of Health ("NIH")'s National Institute of Environmental Health Services ("NIEHS"), described endocrine disruption as "an important emerging public health concern" in testimony before the United States House of Representatives, Committee on Energy and Commerce,

Subcommittee on Energy and Environment. http://www.hhs.gov/asl/testify/2010/02/t20100225a.html. NIEHS is conducting research on the subject and, like FDA, "learning more and more about how these finely tuned systems are sensitive to unanticipated effects from chemical exposures." *Id.* Like CDER, other FDA components, including FDA's Center for Food Safety and Applied Nutrition ("CFSAN") are studying scientific developments on endocrine disruption. For instance, on November 18, 2010, CFSAN hosted a symposium entitled: *Emerging Techniques in the Evaluation of Endocrine Related Endpoints*. The Endocrine Society issued its first-ever scientific statement on endocrine-disrupting chemicals in mid-June 2009. http://www.endosociety.org/journals/ScientificStatements/upload/EDC_Scientific_ Statement.pdf.

B. Antimicrobial and Antibiotic Resistance[10]

58. Since FDA published the 1994 TFM, DNRD twice sought advice from expert panels on another important issue -- the role that antimicrobial products may play in the development of antimicrobial and antibiotic resistance. In January 1997, FDA held a joint meeting of the Nonprescription Drugs and Anti-Infective Drugs Advisory Committees. At that meeting, FDA sought advice on the clinical significance and implications of some laboratory data that demonstrated antimicrobial and antibiotic resistance. The joint committee concluded that, at the time, the data were not sufficient to take any action on the resistance issue but recommended that FDA work with industry to establish surveillance mechanisms to address antimicrobial and antibiotic resistance. In October 2005, FDA again sought advice on this topic from NDAC at a meeting on antiseptics for consumer use. At that time, some NDAC members

[10] Antimicrobial resistance differs from antibiotic resistance. The latter is more likely a concern in hospital or medical settings.

expressed concern about the societal consequences of the pervasive use of consumer antimicrobial products (not limited to drug products).

59. Since October 2005, DNRD has continued to evaluate the available data concerning the possibility that antiseptic use may contribute to the development of antimicrobial and antibiotic resistance. FDA has reviewed all available literature correlating reduced susceptibility to antibacterial active ingredients and antibiotic resistance and exposure to either triclosan or triclocarban. Presently, numerous studies that have evaluated cross-resistance between antiseptics and antibiotics suggest that bacteria can develop altered susceptibilities to both antiseptics and antibiotics in the laboratory setting. FDA is considering the clinical relevance of these laboratory studies and believes that the potential for antiseptics to contribute to changes in antibiotic susceptibility warrants further evaluation.

60. FDA continues to examine antimicrobial and antibiotic resistance through its ongoing review of newly published literature and as a co-chair to the Interagency Task Force on Antimicrobial Resistance, which was created in 1999 to develop a national plan to combat antimicrobial resistance.[11] *See* Public Health Action Plan to Combat Antimicrobial Resistance, http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf.

C. Consumer Antiseptics:
New Dosage Forms, Increased Exposure, and Changes in Use Patterns

61. New dosage forms, increased exposure to a wide-variety of antimicrobial consumer products aside from drug products, and changes in use patterns also have caused FDA

[11] FDA co-chairs the task force, along with the Centers for Disease Control and Prevention and the National Institutes of Health. The Task Force also includes the Agency for Healthcare Research and Quality, Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, and the Agency for International Development.

to reevaluate the 1994 tentative conclusions on safety and effectiveness for all antiseptic ingredients subject to the monograph.

62. New dosage forms of topical antiseptic drug products began to appear on the market over the last decade, including handwashes and hand rubs in varying forms (*e.g.*, gel, spray, liquid, foam). Hand rubs are sometimes used as an alternative to soap and water or a replacement when soap and water is unavailable. Unlike traditional soaps, these products are applied directly to the hands and are not washed away. Consumer awareness about maintaining hand hygiene, concerns about the spread of infectious diseases, endorsement by public health agencies, and the convenience of these products appear to have driven sales of these products. *See, e.g.*, Centers for Disease Control, Clean Hands Campaign, http://www.cdc.gov/cleanhands/. At the same time and perhaps for some of the same reasons, antibacterial household goods and other consumer products, including hand soaps containing triclosan, increased in prevalence.

63. In light of increased exposure to topical antiseptic drug products, FDA is concerned about the potential long-term impact of these substances on human health and, as discussed below, the environment. In the midst of evolving science, the agency is working to qualify these impacts. The long-term effects of exposure to these substances in a wide-range of consumer antiseptic products remains unknown. *See also, e.g.*, Centers for Disease Control, Triclosan Fact Sheet, http://www.cdc.gov/exposurereport/Triclosan_FactSheet.html ("The human health effects from exposure to low environmental levels of triclosan are unknown. . . . More research is needed to assess the human health effects of exposure to triclosan.").

64. To aid in the collection of additional data on long-term dermal exposure, in May 2008 FDA nominated triclosan to NIH's National Toxicology Program ("NTP") through FDA's

National Center for Toxicological Research ("NCTR").[12] *See* http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/triclosan_508.pdf. NTP's ongoing studies on triclosan began in February 2010 and include a dermal carcinogenicity study along with a series of toxicokinetic studies designed to provide data on the effects of long-term triclosan exposure. As with the agency's endocrine-disruption review, FDA plans to seek data through future rulemakings on antimicrobial products to address any data gaps identified during this work.

65. The 1994 TFM's safety and efficacy considerations did not account for increased exposure to various consumer antiseptics or new antiseptic drug products of varying dosage forms for which different safety and effectiveness standards may apply.

D. Environmental Exposure

66. New questions also have arisen as a result of increased environmental exposure to topical antiseptic drug products, including products that contain triclosan and triclocarban. The first influential review of the effect of pharmaceuticals in personal care products on the environment was published in 1999. Christian G. Daughton et al., *Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?*, Envtl. Health Perspectives 907 (1999) (attached as Exhibit 43). Presently, scientists are beginning to study the presence of these substances in the environment, potential accumulation in human and animal tissues (bioaccumulation), the possible breakdown of such substances into potentially harmful by-products, and any resulting biological activity. FDA directed its attention to this issue in 2007, when it began collaborating with EPA to assess the impact that active ingredients in antiseptic drug products have on the environment.

[12] NTP's studies are being conducted at FDA/NCTR under an Interagency Agreement between NIEHS/NTP and FDA/NCTR. Information about the studies can be found on NTP's website: http://ntp.niehs.nih.gov/index.cfm?objectid=DE0AFF5F-1EC9-2924-10CC7FC39F2671C4.

67. FDA has reviewed much of the literature available on long-term, low-dose effects of triclosan exposure on the environment, including the effects of triclosan on aquatic organisms. Further, FDA has reviewed the environmental assessments on triclosan associated with EPA's 2008 re-registration eligibility decision ("RED") for pesticide uses of triclosan.[13] EPA's RED required label changes to triclosan products for manufacturing use to remind applicable pesticide producers and users of their obligations with respect to effluent discharges.

68. Although it is not within FDA's purview to assess or set drinking water standards for water contaminants, FDA is working with EPA to perform these assessments and address the sources of triclosan in the environment. Measurements of triclosan in finished drinking water are generally very low (with a maximum detection level of only 43 nanograms/liter). FDA understands that EPA's current view is that triclosan and triclocarban residues do not occur in water at levels approaching levels of health concern.

69. FDA continues to collaborate with EPA and further study the environmental impact of all active ingredients subject to the monograph. To stay apprised of the rapidly developing scientific research in this area, earlier this year, FDA published a request for data and information regarding the potential environmental impact of certain OTC monograph ingredients, including triclosan. 75 Fed. Reg. 7606 (Feb. 22, 2010) (attached as Exhibit 40). FDA will consider whether any data and information received and the agency's ongoing environmental review should be considered as part of the monograph for topical antimicrobial drug products.

[13] EPA regulates pesticide uses of antimicrobials, including triclosan, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), http://www.epa.gov/pesticides/reregistration/REDs/factsheets/triclosan_fs.htm.

IX. Progress on 1994 TFM Before Safety Concerns Arose

70. Well before the recent safety concerns discussed above came to FDA's attention, and after publishing the 1994 TFM, the agency diligently worked to finalize the monograph for Health-Care Antiseptic Drug Products. Several obstacles, however, prevented FDA from issuing a final monograph in the years immediately following issuance of the 1994 TFM.

71. The 1994 TFM comment period closed on February 13, 1996, over a year and a half after FDA issued the 1994 TFM. Initially, FDA received 50 submissions, many voluminous, before the comment period closed. In total, the public submitted over 40 volumes of comments, data, and other information to FDA in response to the 1994 TFM, totaling well over 10,000 pages.

72. Because parties with highly polarized interests submitted comments that assumed conflicting and antagonistic positions, the comments raised issues that required careful, detailed explanations and eluded simple and speedy resolution. DNRD reviewed all comments, rebuttal comments, and data and information submitted in response to the 1994 TFM on a rolling basis and kept apprised of other newly available data. DNRD identified specific medical, scientific, policy, and legal issues that needed resolution before a final monograph could issue. Among other FDA component offices, DNRD consulted with CDER's Office of Policy, Office of Regulatory Policy, Office of Pharmaceutical Sciences (environmental issues), and Office of Chief Counsel to resolve issues pertaining to ingredient classification, drug testing and formulation, and drug labeling, among others. As is typically the case with such lengthy, complex, and contentious OTC Drug Review rulemakings, it took FDA several years to resolve the many issues raised in the submissions.

73. On May 29, 2003, after receiving another 54 submissions and 16 Citizen Petitions, FDA reopened the record for the monograph. *See* 68 Fed. Reg. 32003 (May 29, 2003). FDA found good cause for the agency to consider new data and information relevant to the final classification of active ingredients and the testing criteria outlined in the 1994 TFM. The rulemaking remained open until August 27, 2003, during which time FDA received an additional 56 submissions and another Citizen Petition. 68 Fed. Reg. at 32003. The comments pertained to the agency's tentative conclusions on safety and effectiveness for many of the active ingredients considered as well as many other aspects of the monograph including the proposed effectiveness criteria, testing requirements, and labeling.

74. The comment review process presented unique challenges to DNRD due to the complexity, length, and evolving nature of the science underlying the monograph. After issuance of the 1994 TFM, DNRD sought advice from expert review panels on four separate occasions. In addition to the January 1997 NDAC meeting on antimicrobial and antibiotic resistance and the October 2005 NDAC meeting on consumer antiseptics discussed in paragraph 58 above, DNRD consulted NDAC on other important monograph issues as they arose.

75. In July 1998, in response to comments to the 1994 TFM, FDA held an NDAC meeting to discuss performance expectations and testing requirements for topical antiseptic drug products used by healthcare professionals. NDAC recognized concerns raised by manufacturers that FDA needed to revise the final formulation testing it proposed in the 1994 TFM. In March 2005, NDAC recommended that FDA make numerous changes to the 1994 TFM's testing design requirements. FDA has since addressed this issue internally, but has redirected its attention to consumer antiseptics in recent years, as discussed above.

76. DNRD also reconsidered the effectiveness criteria for topical antiseptic drug products used by healthcare professionals as proposed in the 1994 TFM.[14] In March 2005, FDA held a NDAC meeting to discuss this issue in response to public comment on the subject. After considering study design and surrogate endpoints used to demonstrate the effectiveness of healthcare antiseptics, NDAC unanimously agreed that there was not compelling evidence to change the effectiveness standard for antiseptic drug products used by health care professionals as set forth in the 1994 TFM.

77. NDAC considered the effectiveness standard for consumer handwashes later that year in an October 2005 NDAC meeting. FDA presented its analysis of available data on their risks and benefits. NDAC concluded that there was not adequate evidence to show that consumer handwashes provide an extra benefit over plain soap and water for reducing transmission of or preventing infection. Accordingly, NDAC recommended that FDA use a new effectiveness standard for consumer handwashes, one requiring manufacturers to demonstrate a clinical benefit through a reduction in infections, rather than using the log reduction standard proposed in the 1994 TFM.

78. On Nov 14, 2008, FDA held a public feedback meeting with the Soap & Detergent Association and the Personal Care Products Council Antimicrobial Coalition to discuss new data and information on the effectiveness of antibacterial handwashes. These organizations presented a new study design for effectiveness. NDAC's recommendations, the information obtained during the public feedback meeting, and FDA's analysis are being considered as part of the draft TFM for Consumer Antiseptic Drug Products.

[14] Effectiveness criteria are the minimum standards that a drug product must meet to be considered generally recognized as effective when testing in clinical simulation studies.

79. For the issues arising since the 1994 TFM published and discussed above, FDA has regularly conducted public meetings with interested members of the public, responded to Citizen Petitions, send feedback letters addressing study protocols to industry, collaborated with other agencies, and responded to Congressional and press inquiries.

X. Future Plans

80. FDA continues to review all newly available scientific literature on potential endocrine disruption activity of active ingredients subject to the monograph, antimicrobial and antibiotic resistance, effectiveness data, and the long-term impact of these substances on human health and the environment. Interagency collaborative efforts are ongoing, and FDA/NTP studies of triclosan are in progress. Additionally, DNRD is considering a Citizen Petition relating to the use of triclosan in products regulated by FDA. *See* http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064809f1140 [last accessed, 11/16/10].

81. In light of new data and information now available, FDA is reconsidering its 1994 tentative conclusions, including its previous understanding of triclosan and triclocarban. FDA is working diligently on its proposed rulemaking for Consumer Antiseptic Drug Products. Typically documents that have a significant economic impact, like this proposed rule, take longer to clear through FDA, HHS, and OMB. Without substantial opposition, FDA intends to issue a proposed rule or take other regulatory action as soon as practicable. When published, the public will be given a specified time period to comment on the proposed rule and submit new data. The agency expects to use these comments and data to prepare a final rule on Consumer Antiseptic Drug Products.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

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Executed on: _____, 2010.